REMARKS

Claims 2-7 are pending and under consideration in the present application. Claims 3 is amended herein. Claims 19-21 are canceled herein without prejudice or disclaimer. Claims 22-24 are newly added. Upon entry of the amendments, claims 2-7 and 22-24 will be pending.

No new matter is added with the amendments. The amendments to the specification correct obvious typographical errors. The amendment to claim 3 corrects an obvious typographical error. Newly added claim 22 is supported, for example, by Table F on page 50. Newly added claim 23 is supported, for example, by page 37, lines 16-22. Claim 24 is supported, for example, by page 45, lines 16-18. Accordingly, entry of the amendments is respectfully requested.

Applicants confirm the election with traverse of Group I, drawn to a functional engineered mutant *Aequorea* green fluorescent protein of SEQ ID NO:2.

A. Objections to the Drawings

The drawings are objected to because allegedly Fig 5-1 to Fig 5-28 should be labeled figures 5A to 5AL. Applicants request clarification. Attached as Exhibit A is a Notice of Draftsperson's Patent Drawing Review from related application 09/575,847 in which the draftsperson requested that the figure numbering be changed from 5A-5AT to 5-1 to 5-28 citing MPEP 608.02(w). Accordingly, Applicants request clarification on whether the drawings should be number 5A-5AT or 5-1 to 5-28, and Applicants will make changes if necessary.

A. Objections to the Specification

The specification is objected to because of missing Greek letters. The amendments to the specification herein correct these obvious typographical errors. Accordingly, Applicants respectfully request withdrawal of the objection to the specification.

B. Obviousness-Type Double Patenting

Claims 2-7 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 48 of U.S. Patent No. 5,777,079 (referred to herein as the '079 Patent). Applicants respectfully traverse the rejection. An obviousness-type double patenting rejection is proper where the subject matter of pending claims is not patentably distinct from claims of a commonly owned patent. MPEP §804. A terminal disclaimer can be filed to overcome an obviousness-type double patenting rejection. MPEP §804.02. "Common ownership" is intended to mean that the subject matter which would otherwise be prior art to the claimed invention and the claimed invention, are entirely or wholly owned by the same person(s) or organization(s) at the time the claimed invention was made. MPEP 706.02(I)(2).

Applicants respectfully point out that the present invention is assigned to the Regents of the University of California, Vertex Pharmaceuticals, and The State of Oregon. The '079 Patent is assigned to The Regents of the University of California. Therefore, since there is common ownership with respect to the obviousness-type double patenting, Applicants will file a Terminal Disclaimer disclaiming the terminal part of any patent granted on the above-identified Application No. 10/071,976 that would extend beyond the expiration date of the '079 Patent, if the Double Patenting rejection is reasserted in the next Office Action.

Further, the filing of a terminal disclaimer to obviate a rejection based on nonstatutory double patenting is not an admission of the propriety of the rejection. (MPEP 804.02 citing Quad Environmental Technologies Corp. v. Union Sanitary District, 946 F.2d 870 (Fed. Cir. 1991)). Applicants respectfully assert that the pending claims are not obvious in view of claim 48 of the '079 Patent. An obviousness-type double patenting rejection is analogous to an obviousness rejection under 35 U.S.C. §103, except that the patent principally underlying the double patenting rejection is not considered prior art, and a comparison of the pending claims is made with the cited claims of the reference, rather than with the entire reference. MPEP §804. To establish a *prima facie* case of obviousness there must be some suggestion or motivation in the prior art to make the claimed invention, there must be a reasonable expectation of success, and the prior art reference must teach or suggest all of the claim limitations. MPEP §2142; In re

Vaeck, 947 F.2d 488, 20 USPQ2d, 1438 (Fed. Cir. 1991). The prior art must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. MPEP §2141 citing Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986). A reasonable expectation of success is the standard with which obviousness is determined. Id. Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. MPEP §2141.

The Office Action alleges that embodiments of claim 48 of the '079 patent encompass the embodiments of pending claims 2-7. More specifically, the Office Action alleges that claim 48 of the '079 patent is drawn to any double mutant of SEQ ID NO:2 at positions 65 and 203 of SEQ ID NO:2, whereas the pending claims are limited to an aromatic amino acid substitution at position 203 and the mutation of the serine residue at position 65 to G, T, A, L, C, V, or I.

The Applicants respectfully assert that although the claimed species are encompassed by claim 48 of the '079 patent, claim 48 of the '079 Patent does not recite the specific mutations, or the combinations thereof, recited in the pending claims. A species is patentable even if a genus encompassing the species is known, if the species is not obvious in view of the genus. MPEP §2144.08. As acknowledged in the Office Action, claim 48 of the '079 patent is silent with respect to the specific substitutions recited in pending claim 2. In fact, the entire specification of the '079 Patent with respect to a T203X substitution, only discloses a double mutant, S202F/T203I, and is silent as to an H, Y, W, or F substitution at position 203. Furthermore, the '079 Patent is silent with respect to a double mutant of T203H, T203Y, T203W, or T203F, along with S65G, S65T, S65A, S65L, S65C, S65V or S65I.

Based on X-ray crystallographic studies, the present specification discloses the surprising result that T203 is adjacent to the phenolic end of the chromophore and forms a hydrogen bond with the phenolic hydroxyl of the chromophore (Col. 28, lines 11-14; and Col. 30, lines 2-3). Based on this finding, the present specification reports mutating residue T203 to a polar aromatic

residue so that an additional polarizability would lower the energy of the excited state of the adjacent chromophore. (Col. 30, lines 2-7). Based on claim 48 of the '079 Patent and the single mutant in residue 203 disclosed in the '079 Patent, it is surprising that a T203 aromatic mutant can shift the emission peak of the functional engineered protein to greater than 520 nm, which was previously unattainable for a GFP mutant (Col. 30, lines 8-11).

In addition to the surprising results above, the pending specification provides surprising results regarding the functional engineered fluorescent proteins of claim 3. Claim 3 recites functional engineered fluorescent proteins that were determined to have increased excitation maximum wavelengths, and for some of the engineered fluorescent proteins, increased emission maximum wavelengths as well (Table F (pages 50-51)). Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 2-7 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 48 of U.S. Pat. No. 6,077,707.

It is noteworthy that newly added claims 22-24 are even further distinguishable over the '079 Patent. For example, newly added claim 22 recites functional engineered fluorescent proteins that were identified in the specification as having both an increased excitation maximum wavelength and an increased emission maximum wavelength (Table F). Newly added claim 23 recites a mutant that was specifically identified as forming a particularly effective FRET pair with a T203I mutant donor (page 37, lines 24). Newly added claim 24 provides a specific functional engineered fluorescent protein with altered excitation peaks, and emission peaks above 520 nm, a previously unattainable wavelength for a GFP protein (Col. 30, lines 7-11).

C. Rejection Under 35 U.S.C. § 103

Claims 2-7 stand rejected under 35 U.S.C. §103 as being unpatentable over U.S. Pat. No. 5,777,079 (referred to herein as the '079 Patent) in view of U.S. Pat. No. 5,804,387 (referred to herein as the '387 Patent). Applicants respectfully traverse the rejection.

The Office Action alleges that the '079 Patent teaches variants of the Aequorea green fluorescent protein (GFP) having amino acid substitutions of SEQ ID NO:2 at positions 202 or 203, and position 65. Furthermore, the Office Action alleges that the '079 Patent teaches substitution of Y66 with another aromatic amino acid, substitutions of residues Y145, H148, M153, V163, and N146, and fusion proteins including these mutants. The Office Action acknowledges that the specification does not specifically teach the substitution of T203 to an aromatic amino acid. Regarding the '387 Patent, the Office Action alleges that this patent teaches that the substitution mutants F64L, V68L, and S72A of GFP are brighter than wild type GFP, and therefore would be useful in combination with a T203 mutant that is allegedly expected to have attenuated fluorescence.

The Applicants respectfully assert that the cited references do not teach all of the claim limitations and there is no motivation to combine the '079 Patent with the '387 Patent to obtain the invention of the pending claims. Furthermore, Applicants respectfully assert that the present specification provides surprising results related to the claimed functional engineered fluorescent proteins. The Applicants respectfully assert that the '079 Patent does not teach the specific mutations, or the combinations thereof, recited in the pending claims. As acknowledged in the Office Action, the '079 Patent and the '387 Patent are silent as to an H, Y, W, or F substitution at position 203. Furthermore, the '079 Patent and the '387 Patent do not disclose that residue 203 is in close proximity to the phenolic end of the chromophore. Finally, the '079 Patent and the '387 Patents are silent with respect to a double mutant of T203H, T203Y, T203W, or T203F, along with S65G, S65T, S65A, S65L, S65C, S65V or S65I. Therefore, the combination of the '079 Patent and the '387 Patent do not teach all of the claim elements.

Based on X-ray crystallographic studies, the present specification discloses the surprising result that T203 is adjacent to the phenolic end of the chromophore and forms a hydrogen bond with the phenolic hydroxyl of the chromophore (Col. 28, lines 11-14; and Col. 30, lines 2-3). As a result of this finding, the present specification reports mutating residue T203 to a polar aromatic residue so that an additional polarizability would lower the energy of the excited state of the adjacent chromophore. (Col. 30, lines 2-7). Without relying on the three dimensional

structure data in the pending application, it is surprising that a T203 aromatic mutant can shift the emission peak of the functional engineered protein to greater than 520 nm, which was previously unattainable for a GFP mutant (Col. 30, lines 8-11).

In addition to this surprising result, the pending specification provides surprising results regarding the functional engineered fluorescent proteins of claim 3. Claim 3 recites functional engineered fluorescent proteins that were determined to have increased excitation maximum wavelengths, and for some of the engineered fluorescent proteins, increased emission maximum wavelengths as well (Table F (pages 50-51)).

As indicated above, the Applicants respectfully assert that there is no motivation to combine the '079 Patent with the '387 Patent, despite the Office Action's. First, the Office Action alleges that the '079 Patent provides a motivation to make the new variants of GFP, as the patent allegedly teaches simultaneously using different variants having different colors. Furthermore, the Office Action alleges that the teaching that the conservative mutation of T203I produces desirable changes in fluorescence properties, "clearly indicates" that T203 is close to, and interacts with, the chromophore.

Applicants respectfully assert that results obtained using the T203I mutation do not "clearly indicate" that T203 is close to, and interacts with, the chromophore. First, the characterization of the mutation of a threonine to an isoleucine (i.e. a polar uncharged R group to a hydrophobic R group) as "conservative" is not consistent with the present specification (Page 15, lines 3-8), is not disclosed in the '079 or '387 Patents, and given the polarity and hydrophobicity differences, would not be considered conservative by one skilled in the art. Second, T203 is not close to the chromophore (residues 65 and 66) in the primary sequence of GFP, and the cited patents do not disclose the three-dimensional structure of GFP. Therefore, it would not be expected that residue 203 interacts with the chromophore, without additional biophysical data or three-dimensional structure data. Third, the '079 patent does not conclude that residue 203 is spatially near, or interacts with, the chromophore, based on results with the S202F/T203I mutant. Fourth, regarding fluorescent property changes observed with the T203

mutant, the '387 patent only indicates that residues 203, as well as residues 167 and 202 are "*potentially* close to the chromophore in three-dimensional space." ('387 Patent, Col., 7, lines 51-56)(emphasis added). The fact that residue 203 is close to the phenolic end of the chromophore and forms a hydrogen bond with the phenolic hydroxyl of the chromophore, was not known before the X-ray crystallographic studies of the present application. Accordingly, based on the teachings of the '387 Patent and '079 Patent, it was surprising that a T203 substitution with an aromatic amino acid could increase excitation and emission wavelengths to lengths previously unattainable for GFP. Therefore, Applicants respectfully assert that impermissible hindsight is required to conclude that a previous functional study of a double mutant that included a single substitution of a non-aromatic mutant at position 203 renders obvious substitutions an aromatic amino acid at residue 203, especially given the surprising results for these substitutions disclosed in the pending application.

Even if the previous results based on a T203I substitution reveal that T203 is near the chromophore, and Applicants reiterate that they do not, these results do not provide an expectation that aromatic mutations at T203 would attenuate fluorescence, and that this attenuation would be offset by mutations at positions 64, 68, and 72, as alleged in the Office Action. The Office Action cites the '387 Patent for the motivation to incorporate an additional mutation in GFP at positions 64, 68, and 72 to further enhance the intensity generated from the T203 aromatic mutants. However, neither the '079 nor the '387 Patent provide mutants that include both a T203 mutation and a mutation at residues 64, 68, and 82. Therefore, a skilled artisan would not expect that the resulting functional engineered fluorescent protein would have a longer emission wavelength and an acceptable intensity. Furthermore, based on the teachings of the '079 Patent and the '387 Patent, which are silent as to the three-dimensional structure of GFP and silent as to an aromatic substitution at T203, a skilled artisan would not expect an aromatic substitution at T203 to yield a GFP protein with desirable properties. Finally, the '079 Patent teaches that the S202F/T203I mutant has increased fluorescence, not attenuated fluorescence. ('079 Patent Col. 4, lines 16-19). Accordingly, Applicants respectfully request

reconsideration and withdrawal of the rejection of claims 2-7 under 35 U.S.C. §103 as being unpatentable over the '079 Patent in view of the '387 Patent.

It is noteworthy that newly added claims 22-24 recite functional engineered fluorescent proteins with additional surprising properties. For example, newly added claim 22 recites functional engineered fluorescent proteins that were identified in the specification as having both an increased excitation maximum wavelength and an increased emission maximum wavelength (Table F). Newly added claim 23 recites a mutant that was specifically identified as forming a particularly effective FRET pair with a T203I mutant donor (page 37, lines 24). Newly added claim 24 provides a specific functional engineered fluorescent protein with altered excitation peaks, and emission peaks above 520 nm, a previously unattainable wavelength for a GFP protein (Col. 30, lines 7-11).

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: February 2, 2004

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Form PTO 948 (Rev. 03/01) U.S. DEPARTMENT OF COMMERCE - Patent and Trademark Office Application No. 9/575,847

NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW

The drawing(s) filed (insert date) 12-7-01 are:

A. ☐ approved by the Draftsperson under 37 CFR 1.84 or 1.152.

B. ☑ objected to by the Draftsperson under 37 CFR 1.84 or 1.152 for the reasons indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawing must be sumitted according to the instructions on the back of this notice.

1. DRAWINGS. 37 CFR 1.84(a): Acceptable categories of drawings: Black ink. Color.
   - ____ Color drawings are not acceptable until petiton is granted. Fig(s) ____
   - ____ Pencil and non black ink not permitted. Fig(s) ____
2. PHOTOGRAPHS. 37 CFR 1.84(b)
   - ____ 1 full-tone set is required. Fig(s) ____
   - ____ Photographs may not be mounted. 37 CFR 1.84(e)
   - ____ Poor quality (half-tone). Fig(s) ____
3. TYPE OF PAPER. 37 CFR 1.84(e)
   - ____ Paper not flexible, strong, white, and durable. Fig(s) ____
   - ____ Erasures, alterations, overwritings, interlineations, folds, copy machine marks not accepted. Fig(s) ____
   - ____ Mylar, velum paper is not acceptable (too thin). Fig(s) ____
4. SIZE OF PAPER. 37 CFR 1.84(f): Acceptable sizes:
   - ____ 21.0 cm by 29.7 cm (DIN size A4)
   - ____ 21.6 cm by 27.9 cm (8 1/2 x 11 inches)
   - ____ All drawing sheets not the same size. Sheet(s) ____
   - ____ Drawings sheets not an acceptable size. Fig(s) ____
5. MARGINS. 37 CFR 1.84(g): Acceptable margins:

   Top 2.5 cm Left 2.5cm Right 1.5 cm Bottom 1.0 cm
   SIZE: A4 Size

   Top 2.5 cm Left 2.5 cm Right 1.5 cm Bottom 1.0 cm
   SIZE: 8 1/2 x 11

   Margins not acceptable. Fig(s) ____
   ____ Top (T) ____ Left (L)
   ____ Right (R) ____ Bottom (B)
6. VIEWS. 37 CFR 1.84(h)

   REMINDER: Specification may require revision to correspond to drawing changes.

   Partial views. 37 CFR 1.84(h)(2)
   - ____ Brackets needed to show figure as one entity. Fig(s) ____
   - ✓ Views not labeled separately or properly. Fig(s) 5AB - 5AT
   - ____ Enlarged view not labeled separetely or properly. Fig(s) ____
7. SECTIONAL VIEWS. 37 CFR 1.84 (h)(3)
   - ____ Hatching not indicated for sectional portions of an object. Fig(s) ____
   - ____ Sectional designation should be noted with Arabic or Roman numbers. Fig(s) ____
8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i)
   - ____ Words do not appear on a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s) ____
9. SCALE. 37 CFR 1.84(k)
   - ____ Scale not large enough to show mechanism without crowding when drawing is reduced in size to two-thirds in reproduction. Fig(s) ____
10. CHARACTER OF LINES, NUMBERS, & LETTERS. 37 CFR 1.84(l)
    - ____ Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (poor line quality). Fig(s) ____
11. SHADING. 37 CFR 1.84(m)
    - ____ Solid black areas pale. Fig(s) ____
    - ____ Solid black shading not permitted. Fig(s) ____
    - ____ Shade lines, pale, rough and blurred. Fig(s) ____
12. NUMBERS, LETTERS, & REFERENCE CHARACTERS. 37 CFR 1.84(p)
    - ____ Numbers and reference characters not plain and legible. Fig(s) ____
    - ____ Figure legends are poor. Fig(s) ____
    - ____ Numbers and reference characters not oriented in the same direction as the view. 37 CFR 1.84(p)(1) Fig(s) ____
    - ____ English alphabet not used. 37 CFR 1.84(p)(2) Figs ____
    - ____ Numbers, letters and reference characters must be at least .32 cm (1/8 inch) in height. 37 CFR 1.84(p)(3) Fig(s) ____
13. LEAD LINES. 37 CFR 1.84(q)
    - ____ Lead lines cross each other. Fig(s) ____
    - ____ Lead lines missing. Fig(s) ____
14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(t)
    - ____ Sheets not numbered consecutively, and in Arabic numerals beginning with number 1. Sheet(s) ____
15. NUMBERING OF VIEWS. 37 CFR 1.84(u)
    - ____ Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s) ____
16. CORRECTIONS. 37 CFR 1.84(w)
    - ____ Corrections not made from prior PTO-948 dated ____
17. DESIGN DRAWINGS. 37 CFR 1.152
    - ____ Surface shading shown not appropriate. Fig(s) ____
    - ____ Solid black shading not used for color contrast. Fig(s) ____

COMMENTS FIGURE 5A - 5AT SHOULD BE LABELED AS FIG. ~~5A - 5A-1 5A-2 5A-3 AND ON~~ 5-1, 5-2, 5-3, 5-4 and on, See MEPE 608.02 (u).

10/31/01

REVIEWER [signature] DATE 2-1-02 TELEPHONE NO. 7033058838

ATTACHMENT TO PAPER NO. 16